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Survival Analysis Comparing HIV Infection Status and Time until Diagnosis in Tuberculosis Cases in the United States Foreign-Born Population by Region of Origin, 2005-2015

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Master of Public Health

Epidemiology

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2015

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Abstract

Survival Analysis Comparing HIV Infection Status and Time until Diagnosis in Tuberculosis Cases in the United States Foreign-Born Population by Region of Origin, 2005-2015

By Amanda Lankford

Background: Tuberculosis is an airborne, infectious disease and was the world's leading infectious disease killer in 2016. In the United States, the proportion of tuberculosis cases among the foreign-born population has increased and now accounts for over 60% of the national TB Cases (16,18, 29, 40). It is well known that HIV infection is the primary risk factor for acquiring or progressing to active TB. This study sought to investigate and quantify risk factors in relation to time until TB diagnosis in the foreign-born population among those who are HIV-TB coinfected and those with TB disease alone.

Methods: This analysis used data obtained from the National Tuberculosis Surveillance System (NTSS) from 2005-2015 provided by the Centers for Disease Control and Prevention (CDC). Analysis was restricted to foreign-born individuals, defined as a person not born within the United States or to a parent who was a U.S. citizen and included 46,633 observations. A multivariate analysis was conducted using a Cox Proportional Hazards Model to assess the relationship between time until diagnosis and HIV infection status on the overall foreign-born population and stratified by global region of origin.

Results: Of the 46,663 observations, 3,042 (6.5%) were HIV positive at the time of diagnosis. Five countries represented over half of the TB cases- Mexico (21.9%), Philippines (9.0%), India (F8.0%), Vietnam (6.8%), and China (4.2%). A crude hazards ratio (HR) of 1.14 (95% CI1.10, 1.18) was calculated from a Cox Proportional Hazards model. When stratified out by global region of origin, Africa, Americas, Southeast Asia, Europe, Eastern Mediterranean, and Western Pacific had crude hazard ratios of 1.01 (95% CI0.94, 1.08), 1.05 (95% CI1.01, 1.11), 1.02 (95% CI 0.87, 1.21), 0.99 (95% CI0.70, 1.4), 1.01 (95% CI 0.77, 1.32), and 1.15 (95% CI 0.99, 1.34), respectively.

Conclusions: The findings from this analysis suggest that HIV does not significantly alter the probability of TB diagnosis in the foreign-born population. Future efforts should concentrate on domestic testing and treatment for LTBI in immigrants and refugees from Southeast Asia and Eastern Mediterranean regions.

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Section I: Literature Review

Chapter 1: Tuberculosis

1.1 Infection/Pathogenesis

Tuberculosis (TB) is an infectious disease caused by the *Mycobacterium tuberculosis* (MTB) complex that ranks in the top 10 causes of death for infectious diseases and surpassed HIV/AIDS in global mortality among infectious diseases in 2016 (1). The MTB complex is a group of related bacteria that includes *M. tuberculosis.* There are three other notable bacteria in this complex that are known to cause TB in humans - *M. bovis*, which causes TB in cattle and has been transmitted to humans through unpasteurized milk, *M. africanum,* which is a causative agent found commonly in West Africa, and *M. canetti*, which is principally identified in eastern Africa (2). There are several other members of the MTB complex that primarily affect animals and are not generally considered to be of public health concern. The MTB complex is also unique in that it replicates around 15-20 hours, which is very slow compared to *E. coli* that reproduces every 20 minutes, and it can have a latency period of an entire lifetime (3).

The *M. tuberculosis* bacilli are transmitted via airborne droplet nuclei and spread primarily by coughing, sneezing, and singing of persons with TB disease of the lungs and trachea. The aerosolized particles can stay in the air for long periods of time and cause infection when inhaled into the alveoli of a susceptible host (2). Once inhaled, macrophages ingest the bacilli and initiate a T-cell-mediated immune

response (3). The *M. tuberculosis* bacilli continue to slowly replicate, and are transferred to the lymph nodes via the lymphatic system (4).

TB manifests in humans in two forms- active tuberculosis (or disease) and latent tuberculosis infection. Latent tuberculosis occurs when the infection is sufficiently contained and the person remains free of any symptoms. The immune response initiates formation of protective granulomas that contain the infection and inhibit further reproduction, but do not eliminate it. In persons with latent TB infection, bacilli are located in the middle of the granulomas, but are usually not viable and may never progress to an active disease state (4). Most published references estimate that approximately one-third of the world is infected with tuberculosis, however the lifetime risk of progressing to active tuberculosis is estimated at 10% with the highest level of risk within the first 18 months (4,5). More recent updated estimates suggest that in 2014, 1.7 billion persons, or 23% of the global population, harbored latent TB (6). The granulomas consistent with latent tuberculosis are visible through a chest radiograph, which is frequently used in the assessment of persons with latent TB infection. Recent research in nonhuman primates has suggested that latent TB may have a wider range of subclinical disease than previously thought. A study found that tuberculosis in non-human primates greatly resembles tuberculosis in humans. When examined post-mortem, the lungs showed a continuum of disease states in those who had latent TB. The state of disease ranged from sterilizing immunity, where the infection has cleared completely, to infection contained in granulomas that have active bacilli replication and may or may not have symptoms (5). Thus, some researchers argue that it is

more appropriate to characterize TB on a continuous spectrum rather than in a binary disease state (6).

Most cases of TB occur as pulmonary disease, however extrapulmonary disease is possible in almost any organ (5). Extrapulmonary TB accounts for 15-20% of total tuberculosis cases, half of which occur in persons coinfected with HIV (5). In HIV negative persons, extrapulmonary disease is more common in women and young children, compared with men and adults, respectively (4). HIV infection greatly increases the rate of progression to active TB and the risk for dissemination to extrapulmonary disease, influenced by the underlying state of immunosuppression, thought to inhibit the ability to form granulomas. The risk of dissemination and progression to active TB increases as HIV disease progresses (7). Extrapulmonary TB can occur in as many as 70% of HIV-associated TB cases with CD4+ T-lymphocyte cell counts < 100/μl and often involves multiple sites (7).

1.2 Diagnosis and Treatment

Rapid and effective diagnostics is still a major problem in the control of TB. In 2015, 6.1 million new TB cases were reported to national authorities and to WHO. This number represents 58.7% of the 10.4 million estimated cases (1). Diagnosis of TB is dependent on disease status- latent tuberculosis is tested by either tuberculin skin test (TST) or interferon-γ release assays (IGRA), and active tuberculosis relies on smear microscopy, cultures of *M tuberculosis,* and nucleic acid amplification tests (NAAT). TSTs have been in use since the early 1900s and are used most commonly in low- or middle-resource, high burden settings (4,8). However, TSTs are

nonspecific reactions that can be influenced by a previous BCG vaccine, or cross-reaction with infections due to non-tuberculosis mycobacteria (NTM). In addition, TSTs have a decreased sensitivity and specificity in persons that are immunocompromised, and require examination 24-72 hours after administration (4). Interferon-γ release assays were developed over a decade ago and are just as sensitive and more specific than TSTs, are not influenced by previous BCG vaccination, and do not cross-react with most NTMs. TSTs and IGRAs are not the primary methods used for the diagnosis of active tuberculosis disease, but can be used as adjunctive tests in the diagnosis of tuberculosis in children. Culture of *M. tuberculosis* is required for a definite diagnosis of active disease and for drug susceptibility testing (4). However, the majority of TB cases are in low-income settings in the developing world where, until recent years, diagnosis has relied almost exclusively on smear microscopy. Only 50-80% of culture-confirmed cases produce positive smear microscopy results, but, compared with smear-negative TB cases, smear-positive cases have been shown to be more infectious and more likely to have poor treatment outcomes (4). In contrast, smear-negative TB cases can account for up to 15-20% of disease transmission (4).

Currently, recommended treatment for drug-sensitive, active tuberculosis requires four drugs over the course of six months. The six-month treatment is administered in two phases: all four drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) for the first two months, and a continuation phase of treatment with isoniazid and rifampin for the following two additional months. This treatment regimen is successful in over 95% of cases in trial conditions and over 90% of cases

under TB control programs (8). Treatment is similar for HIV-infected persons, however rifampin is sometimes replaced with rifabutin due to the reduced effectiveness of antiretroviral therapy (ART) when co-administered with rifampin (5). The emergence of multi-drug resistant (MDR) TB and extensively drug-resistant (XDR) TB has required updated treatment recommendations. Treatment for MDR tuberculosis is costly, prolonged, toxic, and poorly tolerated. Treatment usually lasts 18-24 months, but can last for up 30 months, and success rates are only around 50-60% (5,9). Diagnosis and treatment of XDR TB is difficult and usually requires expert consultation. Treatment is similar to MDR TB, however response rates are usually low and fatality rates can be as high as 98% in HIV-infected individuals (5,8). However, because the majority of these cases occur in low-resource settings, access to care is extremely limited for drug-resistant cases. Treatment coverage has been estimated as low as 2% for MDR TB cases and new ethical concerns are being raised about care for individuals in failed XDR treatments (9,10). The emergence of drug-resistant TB and limited access to care increases the risk, accumulation, and transmission of total drug-resistant (TDR) tuberculosis and incurable tuberculosis (failed treatment of XDR TB). In 2009, WHO responded to this concern by passing a resolution for countries to provide universal access to care for resistant strains of TB to help prevent and control transmission and future outbreaks (9).

1.3 Global Burden

TB has been a global public health problem for centuries. In the 1600s, global tuberculosis rates were as high as 1000 cases per 100,000 individuals and remained

the leading cause of death until the early 1900s (3,9). However, the discovery of antibiotics in the 1960s made tuberculosis curable, with treatment success rates above 90% (5). Despite this, tuberculosis still remains a global threat and killed an estimated 1.4 million people in 2015 (1). Fatality rates for individual countries varied between 5% and 20%, showing that diagnostics and access to care are major obstacles in the elimination of TB (1). It remains a disease of poverty, with an estimated 95% of cases occurring in the developing world and lacking appropriate care (11).

In 2016 the World Health Organization (WHO) reported that the global TB epidemic is larger than previously estimated due to new surveillance data from India. In 2015, there were 10.4 million new cases of TB, representing a 1.5% decline from 2014. Six countries accounted for over 60% of incident cases: India, Indonesia, China, Nigeria, Pakistan, and South Africa. Over 580,000 new cases of MDR-TB were reported with 10% being classified as XDR TB. Tuberculosis was responsible for 1.4 million deaths in 2015, of which 400,000 deaths occurred in patients coinfected with HIV (1).

The goal of the Stop TB Partnership and the World Health Organization is to achieve a TB-free world, defined as less than one case per 1 million individuals, by 2050 (1,12,13). The biggest challenges facing this goal include drug resistance, HIV coinfection, and poverty (5). In order to achieve elimination by 2050, incidence rates would need to decrease by almost 20% annually (14). Currently, global incidence is declining by approximately 1.5% each year and incidence rates are still increasing or stable in some parts of the world, mainly in sub-Saharan Africa where

the HIV epidemic is fueling the persistence of TB (5,15). Epidemiologic studies have found associations between TB and noncommunicable diseases, such as diabetes mellitus, substance abuse, and malnutrition, many of which are also associated with lower socioeconomic status (14). Multiple studies have concluded that global elimination by 2050 is not feasible unless efforts are made to deliver research breakthroughs for earlier and active case detection, more effective and shorter treatment regimens, neutralizing latent TB, safe and effective vaccines, and improved economic development of high-burden countries (12,14,15).

1.4 TB in the United States

TB incidence was on a steady decline from 1953 until 1984, and then a 20% increase in TB incidence occurred between 1985 and 1992. During this time period, a 36% increase in pediatric TB diagnoses was observed, which indicates an increase in TB transmission (16,17). From 1993 to 2014, the number of TB cases in the United States has dropped annually. However, for the first time in 15 years, the number of reported cases increased in 2015 to 9,557, an increase of 1.6% from 2014 (18). The TB incidence rate was three cases per 100,000 persons in 2015, which has remained stable since 2013 (19). California, Texas, New York, and Florida accounted for over half of the reported cases in the U.S. for the previous seven years and again in 2015 (19). Additionally, seven states plus the District of Columbia had incidence rates above the national average (18). In the U.S., over 85% of TB cases are inferred to be due to reactivation of untreated, latent infection (18).

As the number of reported incident cases of TB in the United States has decreased, the percentage of cases among foreign-born persons has steadily increased since 1993 (20,21). In 2015, the case rate was 1.2 per 100,000 individuals for U.S.-born persons, whereas the case rate for foreign-born persons was 15.1 per 100,000 persons (18). The number of foreign-born cases now accounts for approximately two-thirds of the total national TB cases. Multiple studies have found that the majority of foreign-born cases are due to activation of LTBI, most likely acquired before entering the United States. TB rates seem to be highest during the first year of entry into the United States among foreign-born persons, however rates are still elevated for persons who have been in the United States long-term (> 5 years) (21). In the 1990s, recommendations were made for only testing for LTBI in foreign-born individuals who have been in the U.S. for less than 5 years (21). However, additional studies over the past decade have shown that foreign-born individuals who have been in the U.S. long-term have TB rates 10-fold higher than U.S. born persons (21).

The prevalence of TB in the United States has decreased substantially since 1993, however the goal of TB elimination is going to require more rigorous control strategies going forward. The leveling of TB incidence and the increase in the number of incident cases in 2015 suggests that current TB control strategies are no longer sufficient (18). Approximately two-thirds of TB cases in the U.S. are among foreign-born persons, in which only 14.4% were suggestive of recent transmission (19). The majority of TB cases among foreign-born individuals occur years after arrival, suggesting reactivation of latent infection (19,22). Decreasing TB incidence

in the United States will only be feasible by expanding detection and treatment of LTBI domestically and improving control efforts on a global scale, especially in the most frequent countries of origin.

1.5 Drug Resistance

Multi-drug resistance tuberculosis (MDR TB) is defined as resistance to at least isoniazid and rifampin and extensively drug-resistant tuberculosis (XDR TB) is resistant to isoniazid, rifampin, any fluoroquinolone, and at least one second-line injectable drug used to treat TB (23). Drug-resistant TB is thought to be a major public health threat because it could reverse the progress made towards reducing tuberculosis prevalence since the 1990s.

In 2015, there were 480,000 cases of MDR TB in the globe and an additional 100,000 cases that were rifampin-resistant and eligible for MDR treatment (1). However, only 20% of the estimated MDR-TB cases were enrolled for treatment. China, India, and Russia together account for over 45% of the total number of MDR-TB cases globally (1). XDR TB was reported in over 117 countries in 2015 and representing 9.5% of MDR TB (1). In the United States, 1.1% of the 9,557 cases were reported with MDR-TB and only one case reported with XDR TB in 2015.(18) The proportion of TB cases that are MDR has consistently been between 0.9-1.3% since 1996 (18). However, the proportion of MDR-TB cases among foreign-born persons compared to U.S.-born persons has increased from 25.3% in 1993 to 86.3% in 2015 (18).

Drug-resistance is becoming a global public health problem. Certain countries such as South Korea and Botswana are seeing increasing incidence in TB and MDR-TB, whereas other countries are seeing decreases in incidence in TB, but increases in MDR TB. High MDR TB incidence rates, defined as more than 3 cases per 100,000 individuals, have been seen in all six WHO regions (23). Additionally, 117 countries reported cases of XDR TB, whereas only 58 countries reported cases of XDR TB in 2010 (1,23). Reversal of the drug-resistance epidemic has been seen in certain countries, mostly small and centralized nations, wealthy nations, or a combination of both (23). Decreasing the rate of MDR/XDR-TB was attributed to increased case finding, susceptibility testing of all reported TB cases, and specialized care for drug-resistant cases (23). In order for this pattern to take effect globally, an increase in laboratory capabilities need to be implanted in the highest-burden and lowest-income settings. In addition, better treatment facilities for MDR and XDR TB will help completion of WHO recommended therapy and thus reduce community transmission.

1.6 TB Screening in U.S. Immigrants and Refugees

Each year, approximately 450,000 immigrants and 50,000-70,000 refugees migrate to the United States (24). Given that TB disproportionately affects the foreign-born population, they remain a high-risk population and require medical screening for targeted treatment and prevention of TB in the United States. Every individual applying for U.S. immigrant or refugee status is required to go through an overseas medical examination. In 1991, the first technical instructions (TI) were

provided for overseas screening of tuberculosis in U.S. bound immigrants and refugees. These instructions relied solely on chest radiographs and sputum smears to diagnose TB (24). In 2007, the technical instructions were updated to include sputum cultures with drug susceptibility testing for diagnosis and directly observed therapy (DOT) for treatment (24).

In 2012, 1,100 cases were diagnosed overseas, with 60% being smear-negative and culture-positive cases (24). These data show increases in sensitivity in the detection of TB cases incoming to the United States once the updated technical instructions were implemented. As a comparison, 7% of recent U.S. immigrants were diagnosed with active TB after a smear-negative diagnosis overseas, whereas the new instructions have decreased the percentage to below 2% (24). Previous studies have shown that overseas screening is a high-yield method for identifying incoming cases of TB to the U.S. and could help in early detection and treatment as a way to decrease the amount of TB cases seen in the U.S. (25).

Chapter 2: HIV

2.1 Overview of Disease

HIV has arguably emerged to become one of the greatest known global health problems of our time, and the cause of acquired immunodeficiency syndrome (AIDS). HIV causes a persistent, life-long infection that deteriorates the immune system and the body's ability to fight off infections. A landmark report, published by CDC on June 5, 1981, of five men with Pneumocystis pneumonia, was the first description of AIDS cases in the United States (26,27). By 1983, the retrovirus was

identified and isolated and in 1984 HIV was determined to be the cause of AIDS (2,26).

HIV is a retrovirus that uses reverse transcriptase to incorporate itself into the host's genome, which makes it almost impossible to cure (26). Its capability of horizontal and vertical transmission (through sexual contact, contact with body fluids through unsterile syringes and needles, blood transfusions, and from mother to infants), coupled with a rapid HIV mutation rate are factors that contribute to its worldwide spread. HIV is believed to originate from a species of non-human primates found in Africa and transferred to humans as early as the 1800s (28). The virus subsequently appears to have spread throughout Africa and eventually to other parts of the world. Post-mortem genetic analysis has found evidence of the virus in individuals who died from the 1970s (28).

As mentioned earlier, HIV is transmitted from person-to-person by contact with infected bodily fluids. The disease has three stages- acute HIV infection, followed by asymptomatic HIV infection, in the absence of opportunistic diseases, and the advanced stage of AIDS (28). About two weeks after infection, individuals will start to experience clinical symptoms similar to mononucleosis: fever, skin rash, and a sore throat (26,28). Antibodies do not appear until 3-6 weeks after infection. This stage is known as the acute illness phase. During this phase, viral load in blood samples can be high and a diagnosis difficult due to lack of antibodies, which makes an individual extremely infectious (26,28). During the next stage, individuals with HIV may be symptom-free, however they remain continuously infectious. Proper antiretroviral treatment (ART) could allow individuals to remain symptom-free as

long as decades and less likely to transmit HIV to other persons (28). With the discovery of combination ARTs, HIV is thought to become less of a rapidly progressive and fatal disease, and more of a chronic, manageable condition in those with proper access to care and treatment (26). The last stage of disease is AIDS. This stage is defined by having CD4+ T-lymphocyte cell counts less than 200/µl (normal is around 1200/µl, with a range of 500-1500/µl) and are prone to opportunistic infections facilitated by underlying immunodeficiency.

2.2 *Global Burden and Variability of Risk Factors*

In 2008, it was estimated that AIDS had claimed 25 million lives and infected another 33 million people (26). In 2015, there were 36.7 million people living with HIV and 2.1 million new cases (29). This is the lowest annual incidence and mortality of HIV since 1991 (30). Worldwide, incidence has dropped 35% since 2000 and mortality has dropped 43% since 2003 (29,30). Since 2013, the proportion of individuals using ART who are living with HIV increased by one-third, mainly in Eastern and Sub-Saharan Africa (30). In those regions alone, use of ART has doubled, reducing AIDS-related mortality to 36% (29).

The distribution of HIV around the world varies greatly. Sub-Saharan Africa alone accounts for two-thirds of the world's HIV infections (26). In 2015, Southern and Eastern Africa accounted for slightly less than half of the new HIV cases, 960,000 of the 2.1 million incidence cases (29). Together, Western and Central Europe and North America accounted for less than 5% of new cases, Asia and the Pacific accounted for 14% of new cases, Western and Central Africa accounted for

20% of new cases, and Latin American and the Caribbean accounted for 5% of new cases. The Middle East and North Africa account for an insignificant amount of cases (~1%). Notably, Eastern Europe and Central Asia increased in the proportion and number of HIV cases from 120,000 (5.5%) in 2010 to 190,000 (9%) in 2015 (29).

In addition to the disease being disproportionately distributed around the world, the modes of transmission and risk factors also varies geographically. Africa carries most of the HIV/AIDS burden and is mostly due to heterosexual transmission. Because AIDS was first described in the West among a mainly homosexual population, initially many did not believe that HIV/AIDS could be transmitted rapidly by heterosexual contact and the Africa epidemic was described as "African AIDS" (26). One theory surrounding why Africa is so disproportionately affected is the cultural norm of males having multiple sexual partners (26). In areas of Europe and U.S., infection is mostly associated with injection drug use (IDU). Because number of cases and rates of infection are low compared to the rest of the world, prevention efforts have slacked and has resulted in an increase in new infections (26). An increase in heterosexual transmission and bisexuality are contributing factors in the rise of new cases seen in Europe (26). Immigration and migration are the main contributors to HIV in Western Europe, representing 75% of heterosexually transmitted cases (26). The spread of HIV in Asia is primarily attributed to injection drug use facilitated by the "Golden Triangle" (the border of Thailand, Laos, and Myanmar), which is one of the world's opioid capitals. However, female sex workers also contribute greatly to the spread of HIV in Southeast Asia (26).

2.3 HIV in the United States

In 2015, the rate of HIV diagnosis was 12.3 per 100,000 individuals in the United States (31). The rate has been decreasing overall since 2010, however the rate for persons aged 25-29 increased and the rate for persons aged 20-24 years remained stable (31). The rate for American Indian/Alaska Natives also increased to 8.8 per 100,000 individuals. Blacks/African Americans and Hispanics have the highest rate of infection with 44.3 and 16.4 per 100,000 individuals, respectively (31). Males represent the highest HIV burden in the United States, accounting for 81% of all HIV cases. HIV diagnoses are not evenly distributed by region. The South has the highest rate of infection at 16.8 per 100,000, compared to 11.6 per 100,000 in the Northeast, 9.8 per 100,000 in the West, and 7.6 per 100,000 in the Midwest (31).

Globally, the U.S. accounts for only 0.6% of all prevalent HIV infections. However, the U.S. has the highest burden among other Western nations (26). Canada accounts for half the prevalence of infections compared to the U.S. (0.3%), and the UK and Sweden have one-third the prevalence at 0.2%. Spain accounts about the same prevalence as the U.S (26).

Approximately 12-13% of the United States population is comprised of individuals born in another country (32,33). Approximately one in every six persons diagnosed with HIV was born outside the United States, and in some cities up to one-third of HIV infections are in foreign-born individuals (34). In number of infections, individuals from the Caribbean have consistently had the highest

percentage of HIV infections and African-born persons have the highest rates of HIV infection among foreign-born persons (33,34). Males represented a significantly less percentage of HIV infections in foreign-born cases (33). Of HIV infections in Asians, over 64% were foreign-born, compared to only 3.3% of HIV infections in Whites, 10% of HIV infections in Blacks, and 42.2% of HIV infections in Hispanics (33). Overall, foreign-born persons account for approximately 16% of HIV diagnoses in the United States. A previous study conducted in New York City found that acquisition of HIV occurred in the United States for 61% of diagnoses. Individuals from Africa and South America had the highest probability of U.S. acquisition at 34% and 76%, respectively.

There are three major differences in the epidemiology of HIV among foreign-born persons compared to U.S.-born persons. Foreign-born persons have a higher percentage of transmission attributed to heterosexual contact. In 2012 heterosexual contact accounted for only 27.2% of HIV transmission in U.S.-born persons, whereas heterosexual contact accounted for 39.4% of HIV transmission in foreign-born persons (33). Also, women are more affected by HIV in the foreign-born population compared to the U.S.-born population, particularly among persons born in Africa (33,35). As a consequence, perinatal infection is more likely in the foreign-born population (33). Lastly, compared with U.S.-born, diagnosis rates are significantly lower in the foreign-born population (34,35). Diagnosis rates for foreign-born persons and U.S-born persons are estimated to be 38 and 53 per 100,000 individuals in 2015, respectively (36).

Chapter 3 Tuberculosis and HIV Coinfection

3.1 Increased Risk

Tuberculosis and HIV are known as a syndemic, a term used by medical anthropologists to label the synergistic interaction of two or more coexistent diseases and resultant excess burden of disease (37). Most of the immune response to tuberculosis is unknown, but research has shown that a cell-mediated response involving CD4 and CD8 cells is needed to control *M. tuberculosis* infection (3). As stated previously, TB infection can be contained through granuloma formation, which isolates the infections and prevents bacterial replication. However, CD4 cells and tumor necrosis factor (TNF) are important mediators in granuloma formation and are significantly depleted with HIV infection (38). Consequently, HIV-positive individuals are at higher risk for extrapulmonary TB whereas the majority of TB infection in HIV-negative individuals is restricted to the lungs. Additionally, tuberculosis has been shown to up-regulate HIV replication, most likely through the release of TNF (38). Tuberculosis infection signals the immune system to release TNF for granuloma formation and hinder bacterial replication, however TNF has been shown to encourage HIV replication within macrophages (38). Thus, the immune response for one infection helps potentiate replication of another infection, leading to a HIV-TB syndemic (38).

After the emergence of human-immunodeficiency virus (HIV) in many countries, tuberculosis became one of the leading opportunistic diseases and an important cause of death in immunosuppressed persons (39). For those who are HIV-infected and with concurrent latent TB infection, the risk of TB disease

progression is 20 times greater than in those who are HIV uninfected (1). This elevation in risk of acquiring TB for HIV-positive individuals is seen early after HIV seroconversion, increasing 2-3 fold during the first 2 years of infection before any major decrease in CD4 cell count (6). In addition, the risk of latent tuberculosis infection progressing to active TB is between 7-10% each year for those who are coinfected with HIV, whereas those who are not coinfected have been estimated to only have a 10% lifetime risk (40).

HIV is the strongest risk factor for progression from latent to active TB. In 2016, 1.2 million of the 10.4 million incident TB cases were coinfected with HIV, representing 11% of the disease burden (1). Most of this burden is in sub-Saharan Africa where four out of the five global cases of HIV-associated tuberculosis are located (9). Tuberculosis is the main cause of death in HIV-infected individuals where TB is endemic (41), and HIV coinfection has a higher risk of mortality than TB infection alone, with an estimated 22% of TB-related deaths worldwide in 2016. (1). Higher mortality rates are seen with MDR TB, and XDR TB and is almost always fatal in HIV-infected individuals (9). Although it is known that HIV is one of the highest risk factors for TB, only 55% of TB diagnoses had a documented HIV test result in 2016 (1).

Approximately one-third of the global population is infected with *M. tuberculosis.* Healthy, nonimmunosuppressed people are able to contain the infection and have a low lifetime risk of progressing to active TB disease. However, HIV-positive individuals have a suppressed immune system and are no longer able to contain the infection and can rapidly progress to active TB disease. Areas where

HIV is endemic have a greater challenge controlling tuberculosis because of the reservoir of TB infection in the human population and their inability to contain the infection. For this reason, WHO adopted the "Three I's" strategy to help combat HIV/TB coinfection: intensified case finding, isoniazid preventive therapy, and infection prevention control (1).

3.2 Clinical Manifestations and Challenges in Diagnosis and Treatment

HIV infection can greatly alter the clinical manifestations of TB and these vary by degree of immunodeficiency. For those with higher CD4 cell counts (>400), symptoms can be similar to pulmonary TB in HIV-negative individuals including cough, fever, night sweats, and weight loss (7). As immunosuppression progresses, TB symptoms become more atypical and diagnostic tests more challenging. Lower CD4 cell counts prevent granuloma formation and are associated with a higher risk of extrapulmonary and disseminated disease, which makes TB diagnosis more difficult for HIV-positive individuals in lower resource settings that primarily rely of sputum for microscopic examination. (7). Additionally, coinfected individuals have a higher chance of smear-negative pulmonary TB with relatively normal chest radiographs, which are the main diagnostic tools in developing countries (42) and some culture-positive HIV-associated TB cases present with no symptoms (7). Given the variability in clinical and radiologic manifestations, culture-confirmed diagnosis of TB has been considered a gold standard in coinfected patients. Given that TB progresses much more rapidly in immunosuppressed individuals and has a higher first-year mortality, a more rapid and accurate diagnostic test is needed for this

population (7). Recent use of Gene Xpert MTB/RIF® has proven useful in increasing the diagnostic yield of TB in persons with HIV (43).

Treatment for drug-susceptible TB is the same in both HIV-positive and HIV-negative individuals. The regimen consists of an intensive two-month phase of four drugs, followed by a 4-6 month continuation phase of isoniazid and rifampin (7). The use of rifamycins is crucial in the treatment of HIV-associated TB, however HIV-infected individuals usually replace rifampin for rifabutin when co-administered with protease inhibitors due to drug-drug interactions (7,44). Starting antiretroviral therapy (ART) while being administered anti-TB drugs has been shown to significantly reduce TB incidence and improve survival (7,44,45), however there is much debate as to when ART should be started. WHO recommends that ART be administered within 2-8 weeks of starting an anti-TB regimen for all HIV-positive TB cases and is beneficial in both high and low- prevalence settings (1). The one exception to starting ART early is for those with TB meningitis, as it substantially decreases survival in an already high-mortality setting (7).

3.3 Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune Reconstitution Inflammatory Syndrome is a phenomenon commonly seen in HIV-associated tuberculosis. It occurs in two forms: paradoxical TB-IRIS and unmasking TB-IRIS. Paradoxical TB-IRIS is described as a clinical deterioration of TB in an individual already being treated for TB on ART because of an exaggerated inflammatory response (42,44). In contrast, unmasking TB-IRIS is a development of TB symptoms from a subclinical infection. Paradoxical TB-IRIS is

more common and occurs in around one-third of coinfection cases (7). Low CD4 cell count, extrapulmonary TB, disseminated disease, and earlier initiation of ART are all associated with development of IRIS (7,42). Symptoms include fever, worsening of pulmonary infiltrates, central nervous system (CNS) disease, hepatitis, abdominal abscesses, serositis, and lymphadenopathy. TB-IRIS is usually treatable with continuation of ART and corticosteroids, but can be fatal when complications arise from CNS disease, airway obstruction, or splenic rupture (7).

Section II: Manuscript

Introduction

Tuberculosis (TB) is an airborne, infectious disease caused by the bacterium *Mycobacterium tuberculosis.* In 2016, TB surpassed HIV in global mortality among all infectious diseases (1). Over the past two decades the number of reported cases of tuberculosis (TB) in the United States has decreased substantially; however, the percentage of cases occurring among foreign-born persons has steadily increased since 1993 (16,18,19,40). In 2015, the case rate was 1.2 per 100,000 individuals for U.S.-born persons, whereas the case rate for foreign-born persons was 15.1 per 100,000 persons (18). The number of foreign-born cases now accounts for approximately two-thirds of the total national TB cases.

TB arises from recent transmission and disease progression, or from activation of remotely acquired latent TB infection (LTBI). Multiple studies have found that the majority of foreign-born cases are attributable to activation of LTBI, most likely acquired in the country of origin and before entering the United States. TB rates seem to be highest during the first year of entry into the United States among foreign-born persons, however rates are still elevated for persons who have been in the United States long-term (> 5 years) (46). In the 1990's, recommendations were limited to testing foreign-born individuals for TB if they had been in the United States for less than 5 years (46). However, studies published over the past decade have documented that foreign-born individuals who have resided in the United States long-term still have rates 10-fold higher than U.S. born persons

(46). Part of this excess in morbidity is partly explained by the rapid decrease of TB incidence among U.S. born persons, whereas TB incidence in foreign-born persons has remained relatively stable.

Although rates of TB have declined in most developed countries, this disease still remains a global health threat. Based on its most recent global report, the World Health Organization (WHO) characterized TB as a leading cause of death amongst infectious diseases (1,39). Globally, 15% of TB case-patients with an HIV test result were HIV-infected in 2015. In the United States, it was estimated that 16.2% of HIV-positive individuals in 2010 were of the foreign-born population (47). Many of these individuals are thought to not have immediate access to healthcare, resulting in a potential underestimation of this fraction. For those who are HIV positive, the risk of acquiring TB is 26-31 times greater than those who are HIV negative (13). In addition, the risk of LTBI progressing to active TB is between 7-10% each year for those who are coinfected with HIV, whereas those who are not coinfected only have a 10% lifetime risk (40).

There have been very few studies on HIV-TB co-infection in the United States foreign-born population. The increased risk of acquiring TB infection or progressing to active TB for immunosuppressed individuals has been well known over the past 20 years. Current research shows that foreign-born individuals are more likely to be diagnosed with HIV than U.S.-born persons (48). In addition, roughly 67% of U.S. TB cases are foreign-born. The purpose of this study is to investigate risk factors and time until TB diagnosis in foreign-born TB patients residing in the United States for those that are HIV/TB co-infected compared to those that are not coinfected.

Specifically, this study will investigate the relationship between HIV infection status and time until diagnosis, measured by the time residing in the United States before TB diagnosis.

Methods

Study Population

This analysis used data obtained from the National TB Surveillance System (NTSS) from 2005 to 2015 collected by the Centers for Disease Control and Prevention (CDC). Healthcare providers and public health agencies are mandated to report suspected and confirmed cases of TB in the United States. Confirmed cases are reported through the Report of Verified Cases of TB (RVCT), which collects information on demographics, laboratory results, and risk assessment. A verified case of TB is one that meets the clinical case definition or is laboratory confirmed or provider confirmed. A clinical case of TB is defined as a positive TST or IGRA, symptoms compatible with tuberculosis, prescribed TB treatment, and a completed diagnostic evaluation.

Analysis was restricted to foreign-born individuals, reported with TB, defined as a person not born within the United States or to a parent who was a U.S. citizen. To be included in the study population, a participant must have a TB diagnosis between January 1, 2005 and December 31, 2015, have a known date of entry into the United States, have no prior episodes of TB, be alive at time of diagnosis, and have a reported country of origin. Our analysis excluded reported cases who did not meet the case definition, a previous diagnosis of TB, no country of

origin recorded in the RVCT, unknown date of entry into the US, and not being alive at the time of diagnosis.

Covariates

The primary exposure of interest was HIV infection status at the time of TB diagnosis and the outcome was time of years lived in the United States until TB diagnosis. Other covariates of interest were clinical and demographic risk factors from the RVCT including age at diagnosis; gender; race/ethnicity; injection drug use; diabetes status; resident of correctional facility or long-term care facility; alcohol use; site of disease (extrapulmonary vs. pulmonary); diagnostic results including culture, smear, tuberculin skin test (TSTO, interferon-γ release assay (IGRA), chest radiograph; and country of origin. Global geographic region of origin and U.S. domestic region of residence was coded according to the definitions set by WHO and the U.S. Census Bureau (Appendix I). Survival time was calculated as the years lived in the United States from the date of entry into the U.S. to the date of TB diagnosis and has been explained elsewhere (Appendix I). Coinfection is defined as having a positive HIV infection at the time of TB diagnosis.

Data Analysis

All analyses were performed using SAS 9.3. Descriptive analysis was performed to determine baseline characteristics of the study population stratified by HIV infection status. Bivariate analyses were performed to determine any underlying associations with the exposure using Pearson's Chi-square tests on

categorical variables and a Wilcoxon sign-rank test of the median for continuous variables.

Kaplan Meier curves were used to estimate crude survival for TB cases stratified by HIV infection and other covariates of interest. A log-rank test was used to assess significance between the two survival curves between comparison groups with an alpha level of 0.05. A multivariate analysis was conducted using a Cox Proportional Hazards Model to assess the relationship between time until diagnosis and HIV infection status on the overall foreign-born population and stratified by global region of origin, modified for other covariates. A final model was determined by backwards elimination and subsequent assessment for confounding. Proportional hazards assumptions were assessed using extended Cox models to test for significant interaction terms with time. The only significant interaction term was found between HIV and sex and the final model controlled for age, race, sex, injection drug use, alcohol use, and diabetes. Violations of the proportional hazards model caused the final model to be stratified by age, race, injection drug use, alcohol use, and diabetes.

Results

Study Population

There were a total of 130,821 reported cases of TB diagnosed in the United States between 2005 and 2015. Of those, 76,974 (58.8%) were foreign-born. Thus, a resulting 46,633 (60.6%) of the reported cases were included in this analysis.

Bivariate associations with HIV status

A total of 3,042 (6.5%) tuberculosis cases were coinfected with HIV at the time of diagnosis (Table 1). HIV-positive individuals had a median of 6 years of living in the United States before TB diagnosis and HIV-negative individuals had a median of 7 years of living in the United States before TB diagnosis ($p=0.03$). The median age of TB diagnosis for coinfected individuals was 40.1 years of age, which is significantly younger ($p<0.0001$) compared to those who were HIV negative at the time of diagnosis who had a median age of 42.6 years. Males made up a significantly larger proportion of coinfected individuals, representing 69.9% of the TB-HIV coinfected population, whereas males only made up 59.0% of those reported with TB but no HIV infection ($p<0.0001$). A larger proportion of blacks were coinfected with HIV compared to those who were diagnosed with TB disease alone (49.1% vs. 16.4%), whereas in Asians a higher proportion of reported TB cases had TB without HIV co-infection, compared to those coinfected with HIV (41.4% vs 10.0%).

Only 0.6% of TB cases reported injection drug use, but the proportion was four-fold higher amongst HIV-positive individuals compared to HIV negative individuals (Table 1). Diabetes was significantly less common in HIV positive TB cases, compared to those who were HIV negative (2.8% vs. 10.2%). Among reported TB cases, there was no significant association between residing in long-term care or correctional facilities at the time of TB diagnosis and HIV infection status. However, HIV-positive individuals had a significantly lower proportion that reported being

homeless within the year preceding TB diagnosis (Table 1). Reported alcohol use was significantly higher in HIV coinfected individuals (11.0% vs. 6.9%).

Geography

Five countries represent over half of the countries of origin for TB cases in this analysis: Mexico (21.9%), Philippines (9.0%), India (8.0%), Vietnam (6.8%), and China (4.2%). Patients born in Mexico had a three-fold higher proportion of HIV coinfected individuals than any of the other top countries of origin (6.6%, Table 3). Patients born in India reported the lowest median years of living in the United States before TB diagnosis (4 years), whereas those born in Mexico, Philippines, Vietnam and China had a median U.S. residence of 10 years, 10 years, 12 years, and 8 years, respectively (Table 3). Persons born in India also had the highest proportion of individuals diagnosed with TB within their first year after arrival (22.2%), compared to the other top countries of birth. In addition, over half of the TB cases in persons born in India were diagnosed within 5 years of living in the United States. The highest proportion of foreign-born TB cases came from the Americas (42.2%), compared to those from Africa, Southeast Asia, Europe, Eastern Mediterranean, and Western Pacific (10.4%, 13.9%, 2.8%, and 25.49%, respectively) (Table 4). A higher proportion of individuals from the African region had HIV coinfection (18.0%) at the time of TB diagnosis than TB cases from any other geographic region. Persons born in the region of the Americas also had a relatively high proportion of HIV positive individuals at the time of diagnosis (9.0%). Persons

originating from geographic regions other than Africa and Americas had 1.4% to 2.4%% HIV coinfection (Table 4).

A plurality of reported TB cases lived in the Southern United States (39.6%, Table 5). The proportion of HIV coinfection significantly differed among geographic region of residence in the United States, with the Northeast, Midwest, South, and West having 7.3%, 5.0%, 8.1%, and 3.8% of TB cases being HIV positive, respectively ($p<0.0001$). The years of residence in the United States prior to diagnosis also differed significantly among domestic region of residence, with the Northeast and the Midwest both having a median of 5 years, the South having a median of 6 years, and the West having a median of 11 years (Table 4).

Kaplan-Meier Curves

The unadjusted Kaplan-Meier curve stratified by HIV status shows a lower survival time for those who are TB-HIV coinfected (Figure 1), and the log-rank test shows that the two curves differ significantly ($p<0.0001$). When stratified by global region of origin, the only survival curves that were statistically influenced by HIV infection status were for TB cases originating in the region of the Americas. (Figures 2-7). Kaplan-Meier curves stratified by global region of origin alone show that the African region has the lowest survival, and Europe and the Western Pacific have the highest survival (Figure 8). The log-rank test shows that these curves are statistically different from one another ($p<0.0001$). Kaplan-Meier curves stratified by age show that survival is lowest in pediatric patients (<15 years of age) and survival increases significantly with age ($p<0.0001$, Figure 8). Blacks have the

lowest survival when stratified by race, followed by American Indians (Figure 9) and the log-rank test shows that survival is significantly different amongst racial groups ($p<0.0001$). The Kaplan-Meier survival curves and log-rank tests also show that females have a lower survival than males ($p<0.0001$, Figure 9), individuals who do not use injection drugs have a slightly lower survival than those who use injection drugs ($p=0.04$, Figure 10), and diabetics have a substantially lower survival than non-diabetics ($p<0.0001$, Figure 11).

Predictors

A crude hazards ratio (HR) of 1.14 (95% CI1.10, 1.18) was calculated from a Cox Proportional Hazards model. When stratified out by global region of origin, Africa, Americas, Southeast Asia, Europe, Eastern Mediterranean, and Western Pacific had crude hazard ratios of 1.01 (95% CI0.94, 1.08), 1.05 (95% CI1.01, 1.11), 1.02 (95% CI 0.87, 1.21), 0.99 (95% CI0.70, 1.4), 1.01 (95% CI 0.77, 1.32), and 1.15 (95% CI 0.99, 1.34), respectively.

Due to violations of the proportional hazards assumption, the final model was stratified by age, race, drug use, excess alcohol use, and diabetes. Additionally, there was significant interaction between HIV infection and sex, so all reported hazard ratios are stratified according to sex. The findings from the multivariable Cox proportional hazards model are shown in Table 6. The hazard ratio comparing TB-HIV coinfection to TB infection alone averaged across global region of origin was 0.94 (95% CI 0.90, 0.99) for males and 1.18 (95% CI 1.1, 1.27) for females. The hazard ratio for sex alone was null. The same model was run within each global

region of origin. The hazard ratio for females was higher than males across all global regions of origin (Table 6). For males, the hazard ratios were 1.07 (95% CI 0.96, 1.19) from the African region, 0.95 (0.90, 1.01) from the Americas region, 0.99 (95% CI 0.82, 1.20) from the Southeast Asia region, 0.77 (95% CI 0.50, 1.19) from the European region, 0.88 (95% CI 0.63, 1.23) from the Eastern Mediterranean region, and 0.92 (95% CI 0.77, 1.09) from the Western Pacific region. For females, the hazard ratios were 1.15 (95% CI 1.04, 1.28) from the African region, 1.18 (1.06, 1.31) from the Americas region, 1.14 (95% CI 0.79, 1.65) from the Southeast Asia region, 2.54 (0.72, 8.88) from the European region, 1.46 (95% CI 0.86, 2.48) from the Eastern Mediterranean region, and 1.14 (95% CI 0.74, 1.76) from the Western Pacific region.

Discussion

The incidence of TB has declined substantially in the United States since the 1990s, however the proportion of TB cases in the foreign-born population has continued to increase over time (18, 19). Additionally, incidence of TB has plateaued with no significant decrease between 2013 and 2015 (17). Thus, efforts to eliminate TB must address the occurrence of TB in the foreign-born population. The goal of this analysis was to describe the epidemiology of HIV-TB coinfection in the United States foreign-born population and determine if the hazard of TB diagnosis from time of entry into the United States differed by HIV infection status. To date, there has not been a survival analysis performed stratifying the foreign-born TB

cases reported in the United States by HIV-TB coinfection and years of residence in the United States until TB diagnosis.

From 2005 to 2015, approximately 6.5% of the diagnosed TB cases in the foreign-born population were coinfected with HIV. Those who were coinfected had a median diagnosis 1 year earlier than those who were not infected with HIV and were also significantly younger at the time of diagnosis. This suggests that coinfection with HIV is associated with an earlier diagnosis when compared to those reported TB cases who are not infected with HIV. As has been observed in the U.S.-born, it also appears that males are disproportionately affected with HIV in the foreign-born population reported with TB. This finding suggests that HIV may be spreading through male-to-male sexual transmission in the U.S. foreign-born population, in contrast to the more commonly accepted heterosexual transmission of HIV in Africa and Southeast Asia (where the majority of foreign-born TB cases originate). The data suggest significant racial disparities in HIV-TB coinfection. The distribution of cases among White, American Indian, Native Hawaiian, and multiracial individuals were similar for HIV-negative and HIV-positive TB cases, however the representation in Blacks and Asians differs greatly based on HIV status. Black or African American individuals represented only 16.4% of TB infection alone, but represented 49.1% of coinfected individuals. Asians represented 41.4% of TB-with no HIV coinfection and 10.0% of TB-HIV coinfected cases. Although the majority of TB cases in the foreign-born population are Asian, they do not contribute significantly to the proportion of TB cases with HIV coinfection; in contrast, blacks are disproportionately affected among HIV coinfected TB cases.

Injection drug use was four-fold higher in HIV-coinfected individuals, which is an established high risk factor for HIV transmission. Targeted efforts for TB control in this population, in addition to HIV control efforts already in place, could help reduce the incidence of both diseases. Diabetes was seen significantly less commonly in the HIV-coinfected population with TB, suggesting that diabetes is not a risk factor associated with HIV-TB coinfection. In our analysis, residence in congregate living, such as long-term care facilities or correctional facilities at the time of TB diagnosis was not statistically associated with HIV coinfection. However previous reports have described institutional transmission of TB, especially affecting HIV-infected persons(23,49). In contrast, a higher proportion of HIV-TB coinfected individuals reported being homeless within the year preceding TB diagnosis. These findings suggest that, in these foreign-born TB cases, HIV is a risk factor associated with TB.

Over half of the foreign-born TB cases originated from five countries- Mexico, Philippines, India, Vietnam, and China. Additionally, over 40% of TB cases come from the Americas region, suggesting that persons born in Mexico contribute to a large portion of TB cases in the U.S. foreign-born population. This is not surprising; Mexico shares the southern U.S. border, reports a higher incidence of TB than the United States, and is a frequent origin of foreign-born persons residing in the United States (50). Mexico also accounted for three-fold as many HIV coinfected individuals as any other top country of origin. To improve TB case detection, treatment, and prevention in persons from Mexico, e targeted testing and treatment for HIV and TB disease should be offered to this immigrant population. The relatively high number

of undocumented immigrants from Mexico suggests that our findings may underrepresent the true burden of these diseases (i.e., TB and TB/HIV coinfection). There were large differences in the median years lived in the United States before diagnosis among the top countries of origin and the global regions of origin. Persons born in India had the lowest median of years living in the United States (4 years) before diagnosis and had over half the TB cases born in from India were diagnosed within the first five years. In contrast, approximately 40-45% of TB cases in the other top countries of origin were diagnosed with TB after 15 years or more of living in the United States. India is the country with the largest number of TB cases reported by WHO. In addition, the relatively low rate of TB-HIV coinfection in foreign-born persons from India could provide opportunities for reliable screening of persons with LTBI who could benefit from treatment to prevent the occurrence of TB disease.

Global regions of origin were coded from reported countries of birth and were defined according the regions used by the World Health Organization. The majority of foreign-born TB cases are from the Americas, which is consistent with the proportion of U.S. immigrants coming from the Americas region. This may also explain why the Southern region of the United States has the highest proportion of TB cases, when compared to the other domestic regions. The majority of HIV-TB coinfected individuals originated in the African or Americas regions, with 18.0% and 9.0% HIV positive rates, respectively. Approximately two-thirds of the global burden for HIV is in Sub-Saharan Africa (23), which explains the higher proportion of HIV-coinfected TB cases. In 2015, Latin America and the Caribbean represented

only 5% of new HIV cases (25). This suggests that the population of TB cases from the Americas is at a higher risk for HIV infection. Alternatively, persons arriving to the United States from the Americas may have a higher HIV-TB coinfection problem than originally thought. Data from Table 3 also suggest a correlation between the median number of years residing in the United States prior to TB diagnosis and the proportion of HIV positive TB cases by region of origin. As previously stated, Africa had the highest proportion of TB cases who were also coinfected with HIV, but had a median of 5 years of residence in the United States before TB diagnosis. In comparison, Southeast Asia had only 2.3% of TB cases with HIV infection and a median of 3 years of residence in the United States before TB diagnosis. These data show that the median number of years lived in the United States before diagnosis differ significantly between regions of origin, but do not correlate with the proportion of TB cases who are coinfected with HIV.

The crude Kaplan-Meier survival curve (Figure 1) stratified by HIV shows an increased probability of TB diagnosis in HIV-coinfected individuals with each year lived in the United States. This supports the understanding that HIV infection helps increase the risk and the rate of progression to active TB disease. It also supports the theory that the majority of TB cases in the foreign-born population are a result of activation of LTBI acquired in their country of origin. If foreign-born TB cases acquired HIV after migrating to the United States, then coinfected individuals might be expected to exhibit a lower "survival" (no TB diagnosis) of TB compared to those who were HIV negative. However, this association is only true for the overall foreign-born population. When stratified by region of origin, there was no statistical

difference in diagnosis probability over years lived in the United States, except for the Americas region. Although the Americas has the highest number of TB cases than any other region, the African region is the most affected by HIV coinfection and should show a more clear distinction. This finding is not well understood and deserves to be investigated further. Kaplan-Meier curves stratified by region of origin show the probability of TB diagnosis over years lived in the U.S. varies according to region of origin. The African region shows a higher probability of TB diagnosis over time, followed by Southeast Asia and Eastern Mediterranean, Americas, and Europe and the Western Pacific. The higher probability of TB diagnosis in Africa can be explained by the higher burden of coinfection. However, the Eastern Mediterranean region shows a high probability of TB diagnosis over years in the U.S but has a low burden of coinfection. Persons reported with TB and originating in Europe exhibit an interesting KM curve, suggesting a plateauing after 25 years of residence in the United States The reason for this observation is unexplained.

The crude hazards ratio estimated from a Cox Proportional Hazards model was 1.14 (95% CI 1.10, 1.18). This suggests a 14% increase in the probability of TB diagnosis each year lived in the U.S. for HIV-coinfected individuals compared to noncoinfected individuals. An adjusted hazards ratio stratified by sex that controlled for age, race, drug use, excess alcohol use, diabetes, and sex was 0.94 (95% CI 0.90, 0.99) for males and 1.18 (95% CI 1.1, 1.27) for females averaged across region of origin. This latter finding is unusual in that it would appear that HIV coinfection could be protective in the probability of being diagnosed with TB each year in males,

but harmful in females. Because HIV is predominantly seen in the community of men who have sex with men, HIV screening in males has increased greatly since the 1990s and thus TB screening may have increased disproportionately in males as a by-product. However, the adjusted hazards ratio for sex alone was null, which negates the theory that sex alone influences the probability of being diagnosed with TB each year lived in the United States. However, when stratified by region of origin, the hazard ratio was higher for females than males in all regions. The only significant difference in the hazard of coinfection compared to TB infection alone was seen in females from the African region. This observation suggests that females originating from Africa are 15% more likely to be diagnosed as HIV-TB coinfected when compared to women with TB but no HIV for each year lived in the United States. The other regions of origin show great overlap in confidence intervals, suggesting that region of origin is mot not statistically correlated with the hazard of coinfection when compared to TB in the absence of HIV infection.

Strengths and Weaknesses

This study is the only known analysis of HIV-TB coinfection in the United States among foreign-born TB cases reported to CDC. The strengths of this study are that it spans a period of ten years and includes data on TB from all over the nation. It also is restricted to the foreign-born population, which nowadays carries much of the TB burden in the United States.

A weakness of this study is that global region of origin was not built into the Cox Proportional Hazards model. A single model was built for the overall foreign-

born population and then applied to each region of origin as a subpopulation. Thus, the model may not have been appropriate for each subpopulation. An additional limitation is not having data on HIV infection from Vermont and California or on immigration status.

Limitations

The data used in this analysis was an already-existing national surveillance database for tuberculosis, not HIV. Because this study was cross-sectional in nature, it was impossible to determine when individuals became HIV positive during the study frame. Individuals could have seroconverted in their home country, limiting our interpretation for the effect of co-infection on time until TB disease. Additionally, some participants may not have disclosed or not known their HIV status at the time of TB diagnosis, in which their HIV status was "unknown". Therefore, this analysis may have an underrepresentation of the amount of TB-HIV coinfected individuals.

Additionally, this analysis was also greatly limited by the amount of data that had to be omitted from Vermont and California. Vermont did not report any data on HIV until 2006 and California did not report data on HIV from 2004-2010, which also contributes to the underrepresentation of TB-HIV coinfected individuals.

Conclusions and Future Directions

The findings from this analysis suggest that HIV does not significantly alter the probability of TB diagnosis in the foreign-born population.. Future efforts should

concentrate on domestic testing and treatment for LTBI in immigrants and refugees from Southeast Asia and Eastern Mediterranean regions. Their low median years residing in the United States before diagnosis is suggestive of LTBI acquired in their country of origin with subsequent disease progression after arrival in the United States. Individuals from European and Western Pacific regions have a higher median (10 years) before being diagnosed with TB, suggesting that they may be acquiring *M. tuberculosis* infection in the United States, or delayed progression of LTBI. Given existing WHO guidance for screening of HIV in persons with TB, this practice can help identify a subpopulation in need of antiretroviral therapy, in addition to TB treatment. Foreign-born TB cases reported in the U.S. have an overall 6.5% rate of HIV infection, with persons from Africa and the Americas having a 2.8-fold and 1.4-fold higher prevalence of HIV coinfection, respectively. These subpoulations of foreign-born TB cases should be targeted for TB and HIV services to optimize treatment outcomes.

References

1. WHO Global Tuberculosis Report 2016. Geneva, Switzerland: 2016.

2. Heymann DL. Control of Communicable Diseases Manual. 20th ed. Washington DC: The American Public Health Association; 2015 637-648 p.

3. Zwerling A, Hanrahan C, Dowdy DW. Ancient disease, modern epidemiology: A century of progress in understanding and fighting tuberculosis. *Am. J. Epidemiol.* 2016;183(5).

4. Frieden TR, Sterling TR, Munsiff SS, et al. Tuberculosis. In: *Lancet*. 2003:887–899.

5. Dheda K, Barry CE, Maartens G. Tuberculosis. *Lancet*. 2016;387(10024):1211–1226.

6. Barry CE, Boshoff HI, Dartois V, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. *Nat. Rev. Microbiol.* [electronic article]. 2009;7(12):845–55. (http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4144869&tool=pmcentrez&rendertype=abstract)

7. Gray J, Cohn D. Tuberculosis and HIV Coinfection. *Semin. Respir. Crit. Care Med.* [electronic article]. 2013;34(1):032–043. (http://www.ncbi.nlm.nih.gov/pubmed/23460004%5Cnhttp://www.thieme-connect.de/DOI/DOI?10.1055/s-0032-1333469)

8. Zumla A, Raviglione M, Hafner R, et al. Tuberculosis. *N. Engl. J. Med.* [electronic article]. 2013;368(8):745–55. (http://www.ncbi.nlm.nih.gov/pubmed/23425167)

9. Lawn SD, Zumla AI. Tuberculosis. *Lancet* [electronic article]. 2011;378(9785):57–72. (http://www.ncbi.nlm.nih.gov/pubmed/21420161)

10. Dheda K, Migliori GB. The global rise of extensively drug-resistant tuberculosis: Is the time to bring back sanatoria now overdue? *Lancet* [electronic article]. 2012;379(9817):773–775. (http://dx.doi.org/10.1016/S0140-6736(11)61062-3)

11. Glaziou P, Raviglione M, Falzon D, et al. Global Epidemiology of Tuberculosis. *Semin. Respir. Crit. Care Med.* 2013;34(1):3–16.

12. Dye C, Glaziou P, Floyd K, et al. Prospects for tuberculosis elimination. *Annu. Rev. Public Health* [electronic article]. 2013;34:271–86. (http://www.ncbi.nlm.nih.gov/pubmed/23244049)

13. WHO Global tuberculosis report 2015. 2015.

14. Dirlikov E, Raviglione M, Scano F. Global tuberculosis control: Toward the 2015 targets and beyond. *Ann. Intern. Med.* 2015;163(1):52–58.

15. Lonnroth K, Castro KG, Chakaya JM, et al. Tuberculosis control and elimination 2010-50: cure, care, and social development. *Lancet* [electronic article]. 2010;375(9728):1814–1829. (http://dx.doi.org/10.1016/S0140-6736(10)60483-7)

16. Cantwell MF, Snider Jr. DE, Cauthen GM, et al. Epidemiology of tuberculosis in the United States, 1985 through 1992. *Jama*. 1994;272(7):535–539.

17. Castro KG, Marks SM, Chen MP, et al. Estimating tuberculosis cases and their economic costs averted in the United States over the past two decades. *Int. J. Tuberc. Lung Dis.* 2016;20(7):926–933.

18. Division of Tuberculosis Elimination. Reported Tuberculosis in the United States. 2017.

19. Salinas JL, Mindra G, Haddad MB, et al. Leveling of Tuberculosis Incidence - United States, 2013-2015. *MMWR. Morb. Mortal. Wkly. Rep.* [electronic article]. 2016;65(11):273–278. (http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=mesx&NEWS=N&AN=27010173)

20. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States. 2016.

21. Ricks PM, Cain KP, Oeltmann JE, et al. Estimating the burden of tuberculosis among foreign-born persons acquired prior to entering the U.S., 2005-2009. *PLoS One*. 2011;6(11).

22. Walter ND, Painter J, Parker M, et al. Persistent latent tuberculosis reactivation risk in united states immigrants. *Am. J. Respir. Crit. Care Med.* 2014;

23. Gandhi NR, Nunn P, Dheda K, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. *Lancet* [electronic article]. 2010;375(9728):1830–1843. (http://dx.doi.org/10.1016/S0140-6736(10)60410-2)

24. Posey DL, Naughton MP, Willacy EA, et al. Implementation of new TB screening requirements for U.S.-bound immigrants and refugees - 2007-2014. *MMWR. Morb. Mortal. Wkly. Rep.* 2014;

25. Liu Y, Weinberg MS, Ortega LS, et al. Overseas Screening for Tuberculosis in U.S.-Bound Immigrants and Refugees. *N Engl J Med*. 2009;23360(4):2406–15.

26. Kallings LO. The first postmodern pandemic: 25 Years of HIV/AIDS. *J. Intern. Med.* 2008;263(3):218–243.

27. Pneumocystis Pneumonia. *MMWR. Morb. Mortal. Wkly. Rep.* 1981;30:250–252.

28. Centers for Disease Control and Prevention. About HIV/AIDS. *HIV Basics*. 2016;(https://www.cdc.gov/hiv/basics/whatishiv.html)

29. Pustil R. UN Global AIDS Update 2016. 2016 S3-11 p.(http://pesquisa.bvsalud.org/portal/resource/pt/mdl-15080170)

30. World Health Organization (WHO). Progress Report 2016. Prevent HIV,Test and Treat All. *Prog. Rep. 2016. Prev. HIV,Test Treat All*. 2016;

31. Centers for Disease Control and Prevention. Diagnoses of HIV Infection in the United States and Dependent Areas, 2015. 2015 1-82 p.(http://www.cdc.gov/hiv/library/reports/surveillance/2011/surveillance_report_vol_23.html)

32. Crawford T, Caldwell G, Bush HM, et al. Foreign born status and HIV/AIDS: A comparative analysis of HIV/AIDS characteristics among foreign and U.S. born individuals. *J. Immigr. Minor. Heal.* 2012;14(1):82–88.

33. Tang T. HIV in Persons Born Outside the United States, 2007-2010<alt-title>HIV in Persons Born Outside the United States</alt-title>. *JAMA J. Am. Med. Assoc.* 2012;308(6):601.

34. Wiewel EW, Torian L V., Hanna DB, et al. Foreign-Born Persons Diagnosed with HIV: Where are They From and Where Were They Infected? *AIDS Behav.* 2015;19(5):890–898.

35. Johnson AS, Hu X, Dean HD. Epidemiologic differences between native-born and foreign-born black people diagnosed with HIV infection in 33 U.S. states, 2001-2007. *Public Health Rep.* 2010;125 Suppl:61–69.

36. Wiewel EW, Torian L V, Nasrallah HN, et al. HIV diagnosis and utilisation of HIV-related medical care among foreign-born persons in New York City, 2001-2009. *Sex. Transm. Infect.* 2013;89(5):380–382.

37. Singer M, Clair S. Syndemics and public health: reconceptualizing disease in bio-social context. No Title. *Med. Anthropol. Q.* 2003;17(4):123–441.

38. Pawlowski A, Jansson M, Sköld M, et al. Tuberculosis and HIV co-infection. *PLoS Pathog.* 2012;8(2).

39. Pecego A, Amancio R, Ribeiro C, et al. Six-month survival of critically ill patients with HIV-related disease and tuberculosis: a retrospective study. *BMC Infect Dis.*

[electronic article]. 2016;16(1):270. (http://www.ncbi.nlm.nih.gov/pubmed/27286652)

40. Centers for Disease Control and Prevention. Latent Tuberculosis Infection: A guide for Primary Health Care Providers. 2014.

41. Lawn SD, Churchyard G. Epidemiology of HIV-associated tuberculosis. *Curr. Opin. HIV AIDS* [electronic article]. 2009;4(4):325–333. (http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=01222929-200907000-00017%5Cnpapers2://publication/doi/10.1097/COH.0b013e32832c7d61)

42. Naidoo K, Naidoo K, Padayatchi N, et al. HIV-associated tuberculosis. *Clin. Dev. Immunol.* 2011;2011.

43. Al-Darraji HAA, Razak HA, Ng KP, et al. The Diagnostic Performance of a Single GeneXpert MTB/RIF Assay in an Intensified Tuberculosis Case Finding Survey among HIV-Infected Prisoners in Malaysia. *PLoS One*. 2013;8(9):1–10.

44. Kwan C, Ernst JD. HIV and tuberculosis: A deadly human syndemic. *Clin. Microbiol. Rev.* 2011;24(2):351–376.

45. Anandaiah A, Dheda K, Keane J, et al. Novel developments in the epidemic of human immunodeficiency virus and tuberculosis coinfection. *Am. J. Respir. Crit. Care Med.* 2011;183(8):987–997.

46. Cain KP, Haley CA, Armstrong LR, et al. Tuberculosis among foreign-born persons in the United States: Achieving tuberculosis elimination. *Am. J. Respir. Crit. Care Med.* 2007;175(1):75–79.

47. Prosser A, Tang T, Hall I. HIV in Persons Born Outside the United States, 2007-2010<alt-title>HIV in Persons Born Outside the United States</alt-title>. *JAMA J. Am. Med. Assoc.* 2012;308(6):601.

48. Myers TR, Lin X, Skarbinski J. Antiretroviral Therapy and Viral Suppression Among Foreign-Born HIV-Infected Persons Receiving Medical Care in the United States: A Complex Sample, Cross-Sectional Survey. *Medicine (Baltimore).* [electronic article]. 2016;95(11):e3051. (http://www.ncbi.nlm.nih.gov/pubmed/26986128)

49. Wells CD, Cegielski JP, Nelson LJ, et al. HIV Infection and Multidrug-Resistant Tuberculosis--The Perfect Storm. *J. Infect. Dis.* [electronic article]. 2007;196(Suppl 1):S86-107. (http://jid.oxfordjournals.org//cgi/content/abstract/196/Supplement_1/S86)

50. World Health Organization. Mexico Tuberculosis Profile. 2015;

Tables

Table 1: Summary statistics for foreign-born TB cases in the United States from 2005-2015 by HIV status at time of diagnosis[a]

	HIV Negative (n=43,591)		HIV Positive (n=3,042)		
Variable	No.	% or (SE)	No.	% or (SE)	p-value[a]
Age at diagnosis (continuous)[b]	42.6	(0.09)	40.1	(0.21)	<0.0001[b]
Years in US (continuous)[b]	7.0	--	6.0	--	0.0315[b]
Years in US (categorical)					
<1	8,327	19.1	567	18.6	<0.0001
1-4	9,844	22.6	712	23.4	
5-9	7,367	16.9	631	20.7	
10-14	5,067	11.6	372	12.2	
15+	12,986	29.8	760	25.0	
Age at diagnosis (categorical)					<0.0001
<15	875	2.0	23	0.8	
15-19	1,852	4.3	20	0.7	
20-24	4,799	11.0	119	3.9	
25-29	5,791	13.3	344	11.3	
30-34	4,926	11.3	513	16.9	
35-39	3,942	9.0	558	18.3	
40-44	3,454	7.9	482	15.8	
45-49	3,085	7.1	380	12.5	
50-54	2,924	6.7	276	9.1	
55-59	2,799	6.4	163	5.4	
60-64	2,394	5.5	86	2.8	
65+	6,750	15.5	78	2.6	
Sex					
Male	25,722	59.0	2,125	69.9	<0.0001
Female	17,861	41.0	916	30.1	
Unknown	8	0.0	1	0.0	
Race					
White	17,366	39.8	1,193	39.2	<0.0001
Black	7,144	16.4	1,493	49.1	
Asian	18,062	41.4	304	10.0	
American Indian	127	0.3	7	0.2	
Native Hawaiian	81	0.2	1	0.0	
Multiracial	462	1.1	14	0.5	
Unknown	332	0.8	30	1.0	

Ethnicity					
Non-Hispanic	27,452	63.0	1,815	59.7	0.0008
Hispanic	16,117	37.0	1,224	40.2	
Unknown	11	0.1	3	0.1	
Global Region					
Africa	3,992	9.2	876	28.8	<0.0001
Americas	17,899	41.1	1,766	58.1	
Southeast Asia	6,345	14.6	150	4.9	
Europe	1,285	3.0	32	1.1	
Eastern Mediterranean	2,350	5.4	54	1.8	
Western Pacific	11,721	26.9	164	5.4	
US Region					
Northeast	5,910	13.6	465	15.3	<0.0001
Midwest	6,080	14.0	318	10.5	
South	16,982	40.0	1,501	49.3	
West	10,949	25.1	431	14.2	
Unknown	3,670	8.4	327	10.8	
Injection Drug Use					
No	43,004	98.7	2,934	96.5	<0.0001
Yes	207	0.5	66	2.2	
Unknown	380	0.9	42	1.4	
Diabetes					
No	39,156	89.8	2,956	97.2	<0.0001
Yes	4,435	10.2	86	2.8	
Resident of Correctional Institute					
No	42,007	96.4	2,939	96.6	0.5744
Yes	1,511	3.5	100	3.3	
Unknown	73	0.2	3	0.1	
Resident of Longterm Care Facility					
No	43,249	99.2	3,012	99.0	0.3154
Yes	302	0.7	28	0.9	
Unknown	40	0.1	2	0.1	

Homeless within last year					
No	42,359	97.2	2,847	93.6	<0.0001
Yes	1,044	2.4	168	5.5	
Unknown	188	0.4	27	0.9	
Excess Alcohol Use					
No	40,232	92.3	2,673	87.9	<0.0001
Yes	3,006	6.9	333	11.0	
Unknown	353	0.8	36	1.2	

[a] Only TB cases alive at diagnosis and no previously reported episodes of TB were eligible.

[b] p-value calculated using Pearson's Chi Square with an alpha of 0.05.

[c] Continuous variable. Reported median and did a Wilcoxon signed-rank test for significance with an alpha of 0.05.

Table 2: Summary statistics on HIV status and years in United States before TB diagnosis by the top 5 countries of origin.[a]

	Mexico (n=10,224)		Philippines (n=4,604)		India (n=3,727)		Vietnam (n=3,187)		China (n=1,967)		
	No.	%	No.	%	No.	%	No.	%	No.	%	p-value[b]
HIV Status											
Negative	9,547	93.4	4,532	98.4	3,662	98.3	3,132	98.3	1,952	99.2	<0.0001
Positive	677	6.6	72	1.6	65	1.7	55	1.7	15	0.8	
Years in US (continuous)[c]	10	--	10	--	4	--	12	--	8	--	<0.0001
Years in US (categorical)[c]											<0.0001
<1	1,259	12.3	838	18.2	826	22.2	422	13.2	371	18.9	
1-4	1,759	17.2	727	15.8	1,081	29.0	472	14.8	385	19.6	
5-9	1,729	16.9	720	15.6	676	18.1	445	14.0	340	17.3	
10-14	1,405	13.7	573	12.5	428	11.5	427	13.4	244	12.4	
15+	4,072	39.8	1,746	37.9	716	19.2	1,421	44.6	627	31.9	

[a] Only TB cases alive at diagnosis and no previously reported episodes of TB were eligible.

[b] p-value calculated using Pearson's Chi Square with an alpha of 0.05.

[c] Continuous variable. Reported median and did a Wilcoxon signed-rank test for significance with an alpha of 0.05.

Table 3: Summary statistics on HIV status and years live in the U.S. before TB diagnosis for cases diagnosed in the United States from 2005-2015 by global region of origin. [a]

	Africa (n=4,868)		Americas (n=19,665)		Southeast Asia (n=6,495)		Europe (n=1,316)		Eastern Mediterranean (n=2,404)		Western Pacific (n=11,885)		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	p-value[b]
HIV Status													
Negative	3,992	82.0	17,899	91.0	6,345	97.7	1,284	97.6	2,350	97.8	11,721	98.6	<0.0001
Positive	876	18.0	1766	9.0	150	2.3	32	2.4	54	2.3	164	1.4	
Years in US (continuous)[c]	5	--	8	--	3	--	11	--	3	--	11	--	<0.0001
Years in US (categorical)													
<1	1,485	30.5	2,934	14.9	1,769	27.2	168	12.8	718	29.9	1,820	15.3	<0.0001
1-4	1,696	34.8	4,207	21.4	1,979	16.3	215	16.3	607	25.3	1,852	15.6	
5-9	868	17.8	3,618	18.4	1,085	16.0	211	16.7	449	18.7	1,767	14.9	
10-14	432	12.7	2,487	12.7	615	9.5	211	16.0	248	10.3	1,446	12.2	
15+	387	8.0	6,419	32.6	1,045	16.1	511	38.8	382	15.9	5,000	42.1	

[a] Only TB cases alive at diagnosis and no previously reported episodes of TB were eligible.

[b] p-value calculated using Pearson's Chi Square with an alpha of 0.05.

[c] Continuous variable. Reported median and did a Wilcoxon signed-rank test for significance with an alpha of 0.05.

Table 4: Summary statistics on HIV status and years lived in the U.S. before TB diagnosis for cases diagnosed in the United States from 2005-2015 by U.S. region of residence. [a]

	Northeast (n=6.375)		Midwest (n=6,398)		South (n=18,482)		West (n=11,3,80)		
	No.	%	No.	%	No.	%	No.	%	p-value [b]
HIV Status									
Negative	5,910	92.7	6,080	95.0	16,982	91.9	10,949	96.2	<0.0001
Positive	465	7.3	318	5.0	318	8.1	431	3.8	
Years in US (continuous)[c]	5	--	5	--	6	--	11	--	<0.0001
Years in US (categorical)									
<1	1,485	30.5	2,934	14.9	1,769	27.2	168	12.8	<0.0001
1-4	1,696	34.8	4,207	21.4	1,979	16.3	215	16.3	
5-9	868	17.8	3,618	18.4	1,085	16.0	211	16.7	
10-14	432	12.7	2,487	12.7	615	9.5	211	16.0	
15+	387	8.0	6,419	32.6	1,045	16.1	511	38.8	

[a] Only TB cases alive at diagnosis and no previously reported episodes of TB were eligible.

[b] p-value calculated using Pearson's Chi Square with an alpha of 0.05.

[c] Continuous variable. Reported median and did a Wilcoxon signed-rank test for significance with an alpha of 0.05.

Figures:

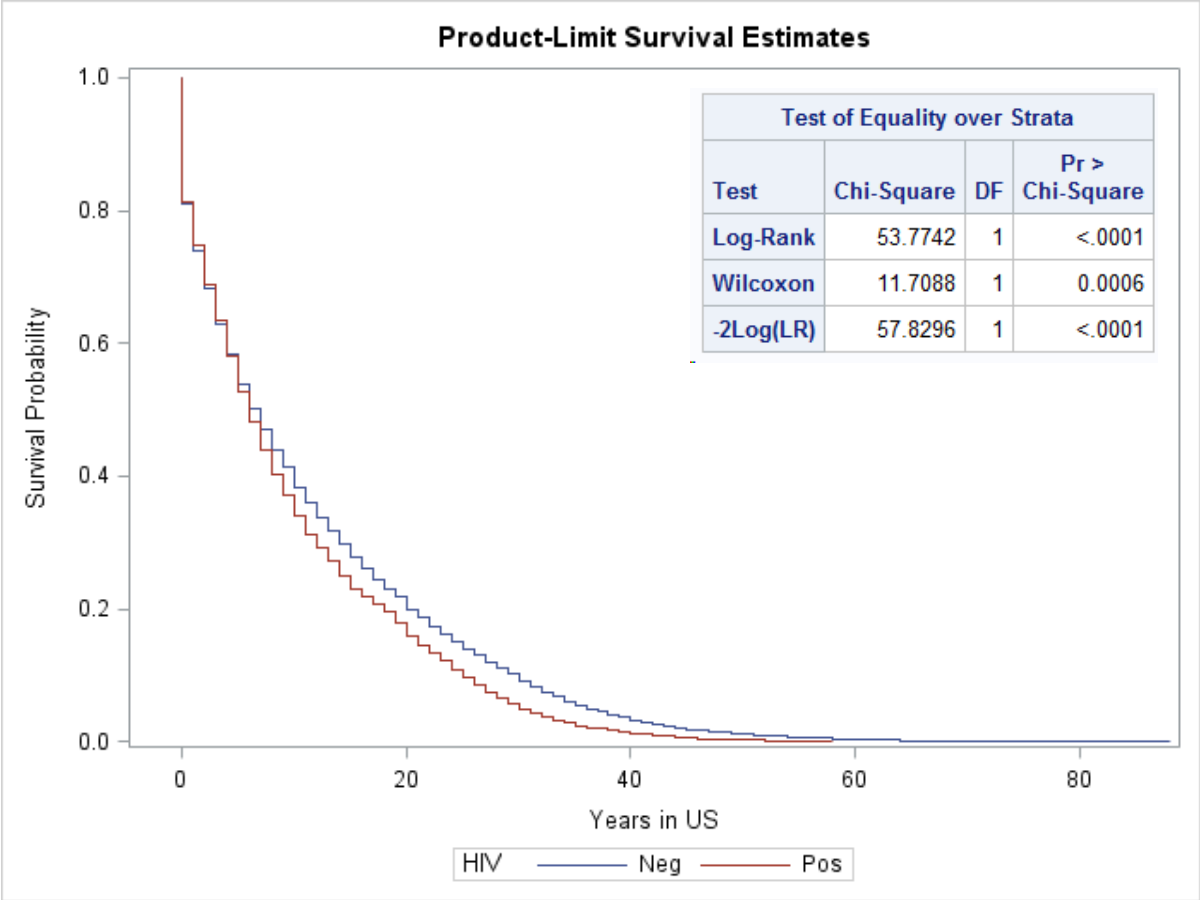


Figure 1: Kaplan-Meier survival curve stratified by HIV status for individuals diagnosed with Tuberculosis from 2005-2015 in the United States foreign-born population. The vertical axis depicts the survival probability and the horizontal axis represents the years lived in the United States prior to diagnosis.

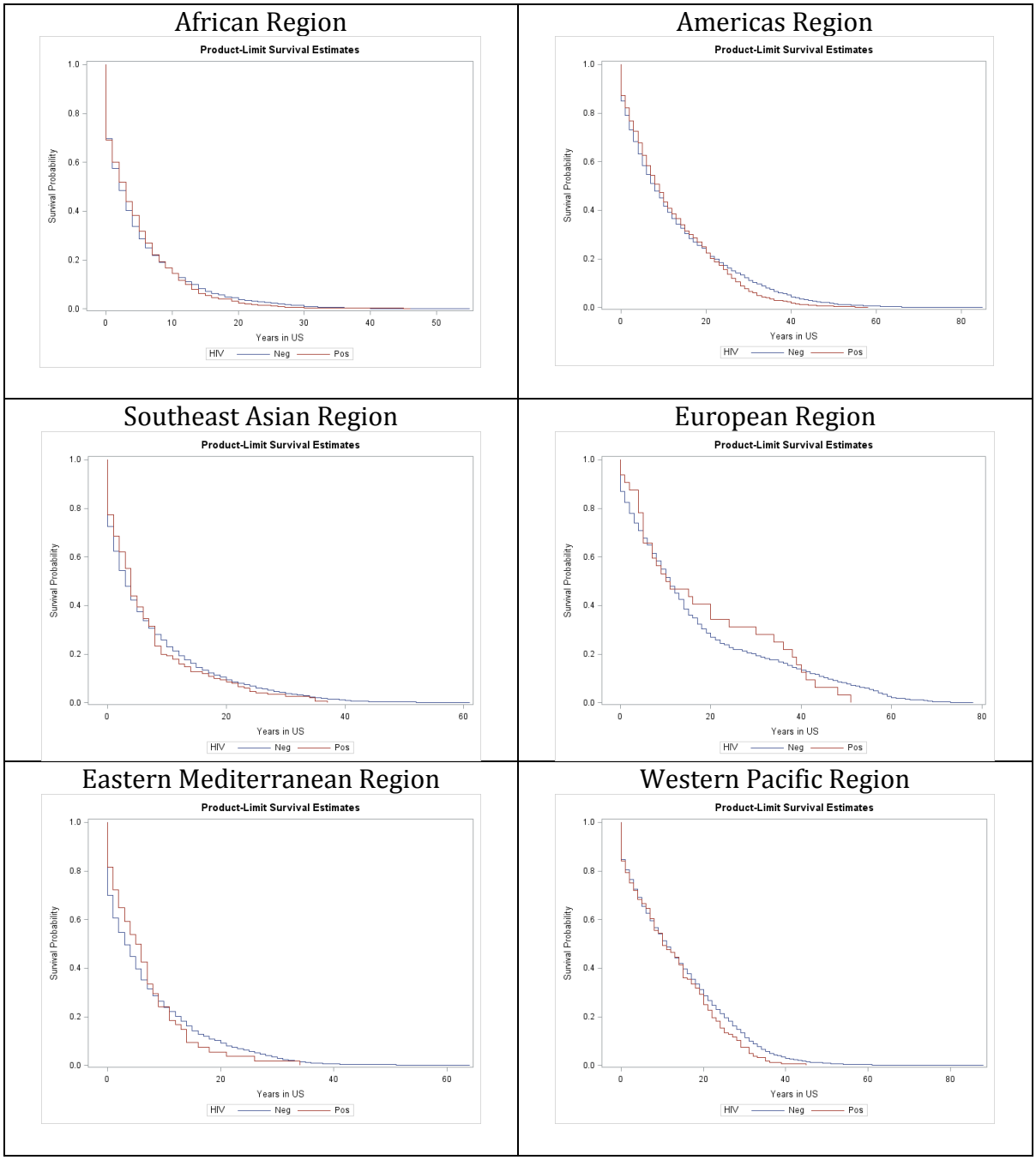


Figure 2: Kaplan-Meier survival curves stratified by HIV status for individuals diagnosed with Tuberculosis from 2005-2015 in the United States foreign-born population separated by country of origin. The vertical axis depicts the survival probability and the horizontal axis represents the years lived in the United States prior to diagnosis.

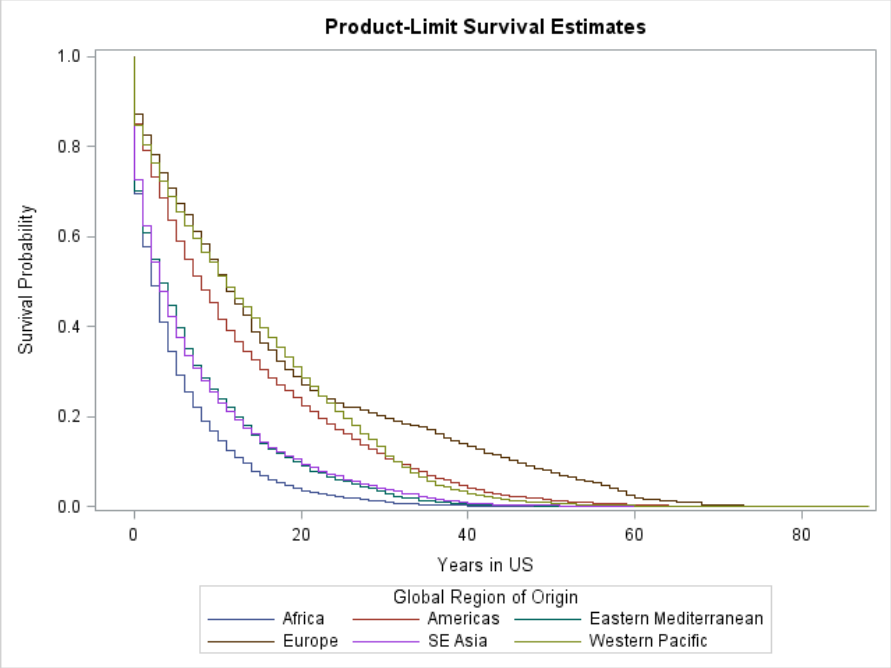


Figure 3: Kaplan-Meier survival curves stratified by global region of origin for individuals diagnosed with Tuberculosis from 2005-2015 in the United States foreign-born population. The vertical axis depicts the survival probability and the horizontal axis represents the years lived in the United States prior to diagnosis.

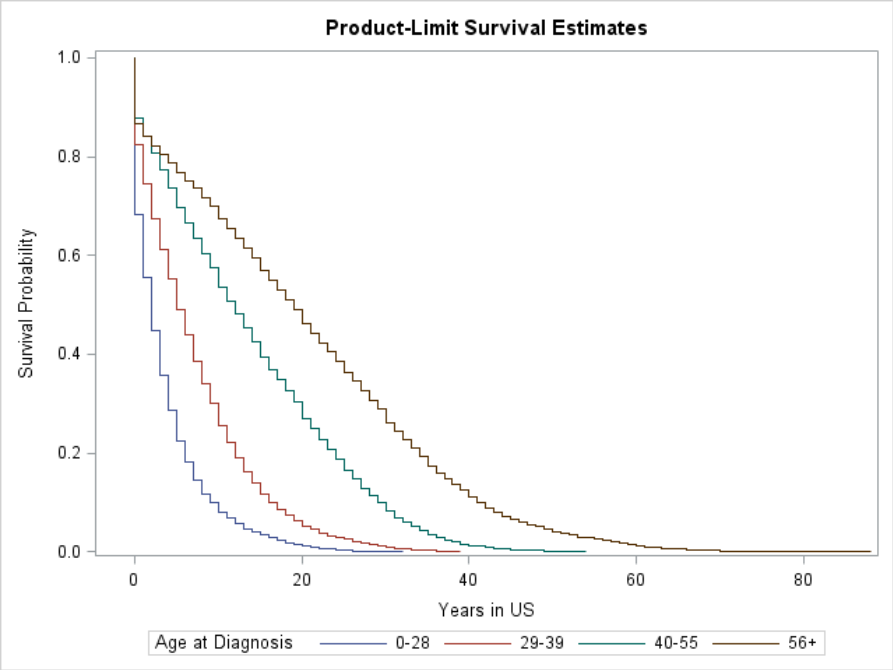


Figure 4: Kaplan-Meier survival curves stratified by age, categorized by quantiles, for individuals diagnosed with Tuberculosis from 2005-2015 in the United States foreign-born population. The vertical axis depicts the survival probability and the horizontal axis represents the years lived in the United States prior to diagnosis.

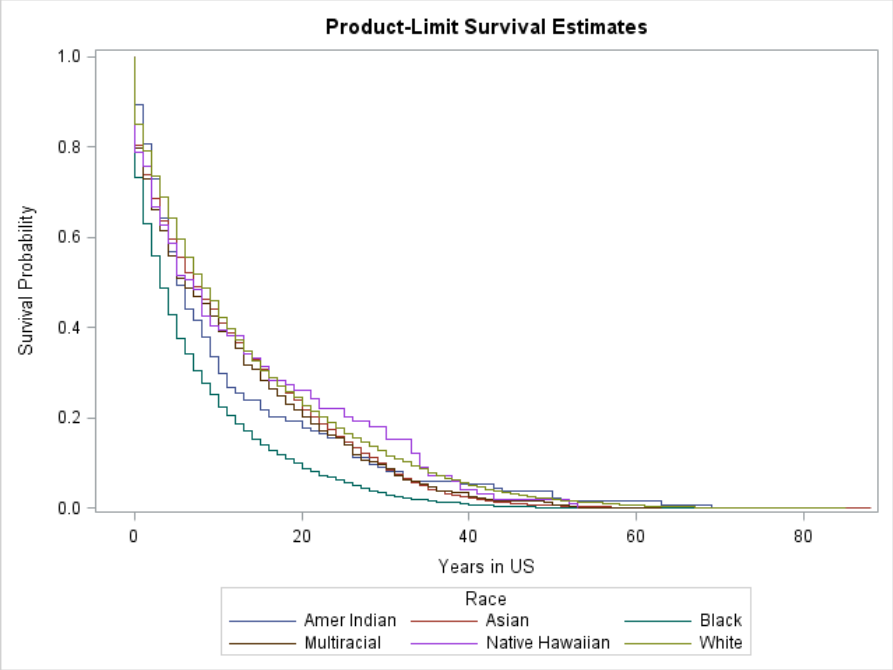


Figure 5: Kaplan-Meier survival curves stratified by race for individuals diagnosed with Tuberculosis from 2005-2015 in the United States foreign-born population. The vertical axis depicts the survival probability and the horizontal axis represents the years lived in the United States prior to diagnosis.

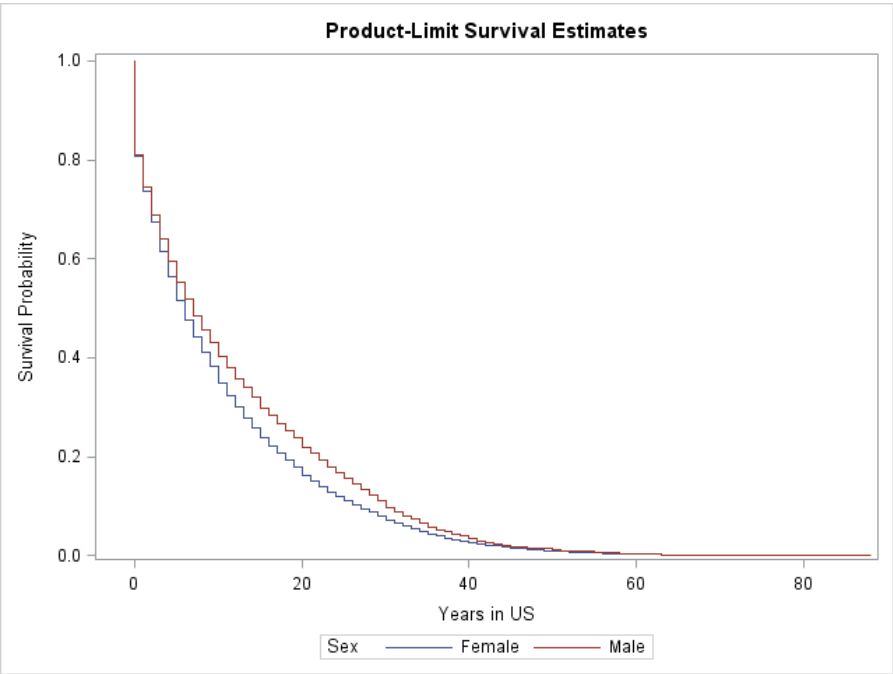


Figure 6: Kaplan-Meier survival curves stratified by sex for individuals diagnosed with Tuberculosis from 2005-2015 in the United States foreign-born population. The vertical axis depicts the survival probability and the horizontal axis represents the years lived in the United States prior to diagnosis

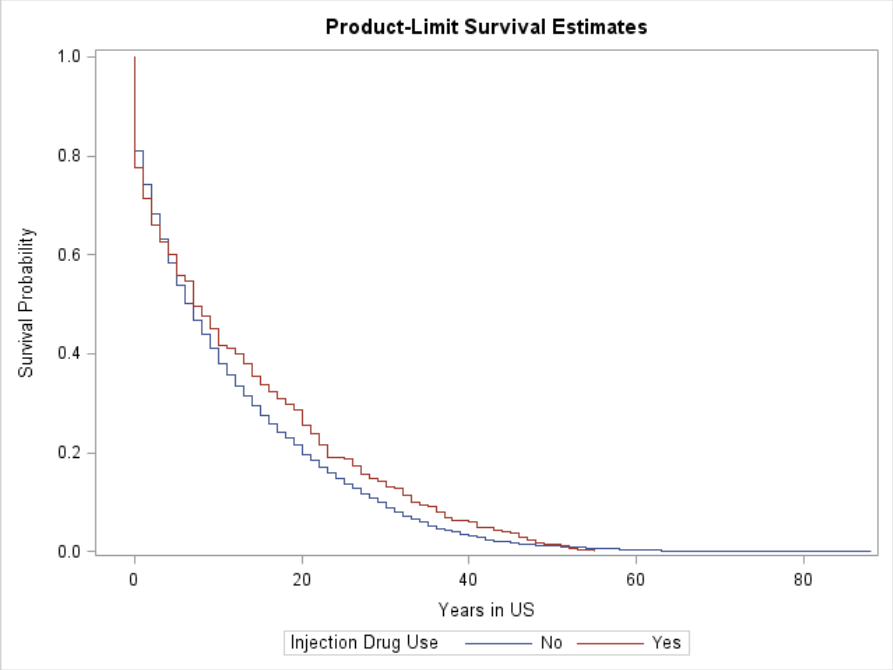


Figure 7: Kaplan-Meier survival curves stratified by injection drug use for individuals diagnosed with Tuberculosis from 2005-2015 in the United States foreign-born population. The vertical axis depicts the survival probability and the horizontal axis represents the years lived in the United States prior to diagnosis.

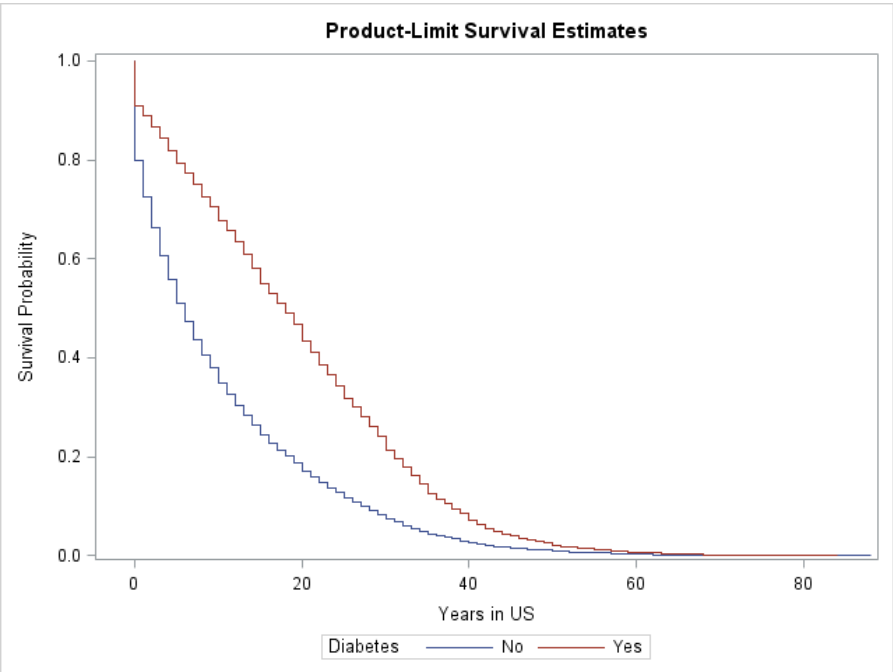


Figure 8: Kaplan-Meier survival curves stratified by diabetes for individuals diagnosed with Tuberculosis from 2005-2015 in the United States foreign-born population. The vertical axis depicts the survival probability and the horizontal axis represents the years lived in the United States prior to diagnosis.

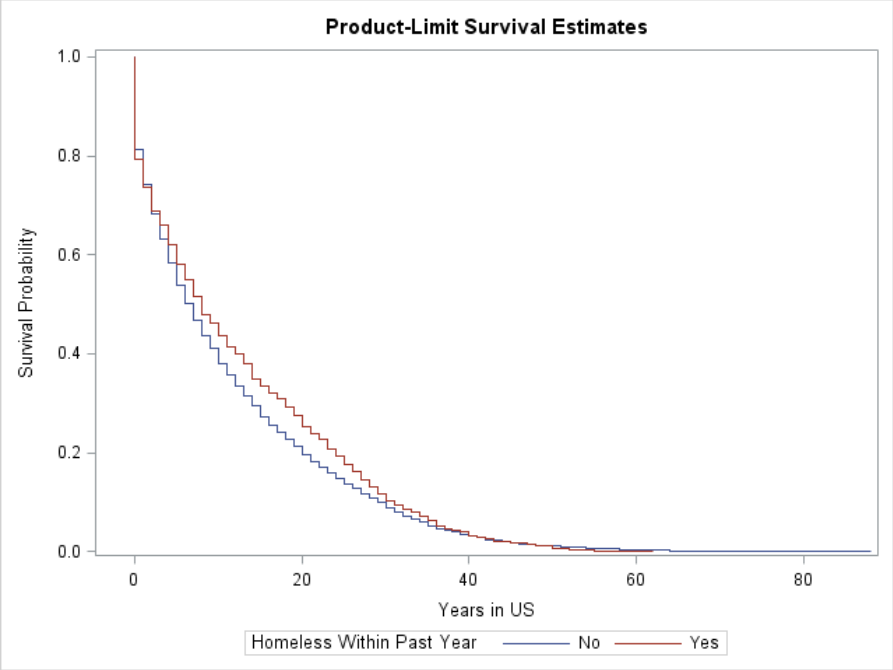


Figure 9: Kaplan-Meier survival curves stratified by homelessness for individuals diagnosed with Tuberculosis from 2005-2015 in the United States foreign-born population. The vertical axis depicts the survival probability and the horizontal axis represents the years lived in the United States prior to diagnosis.

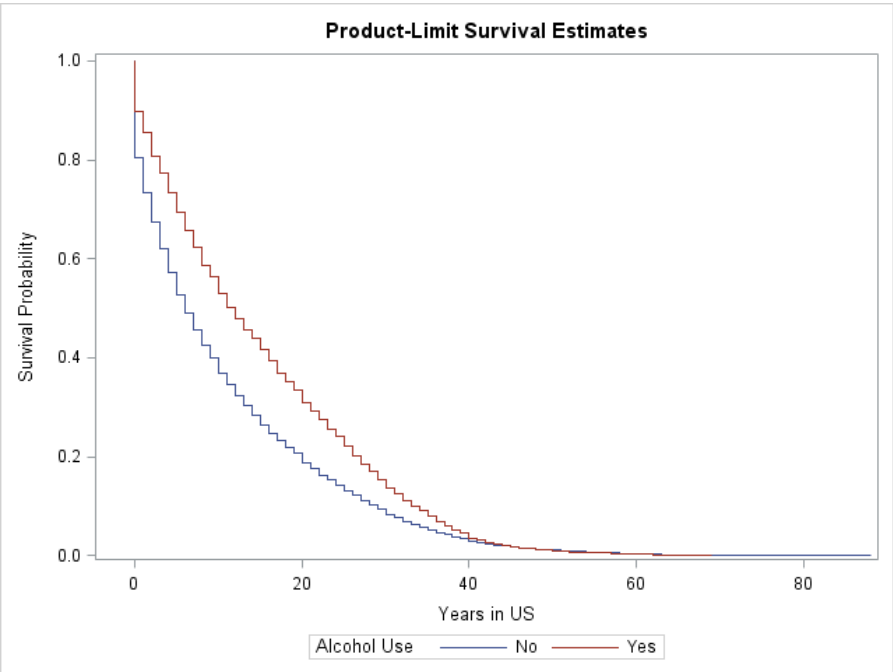
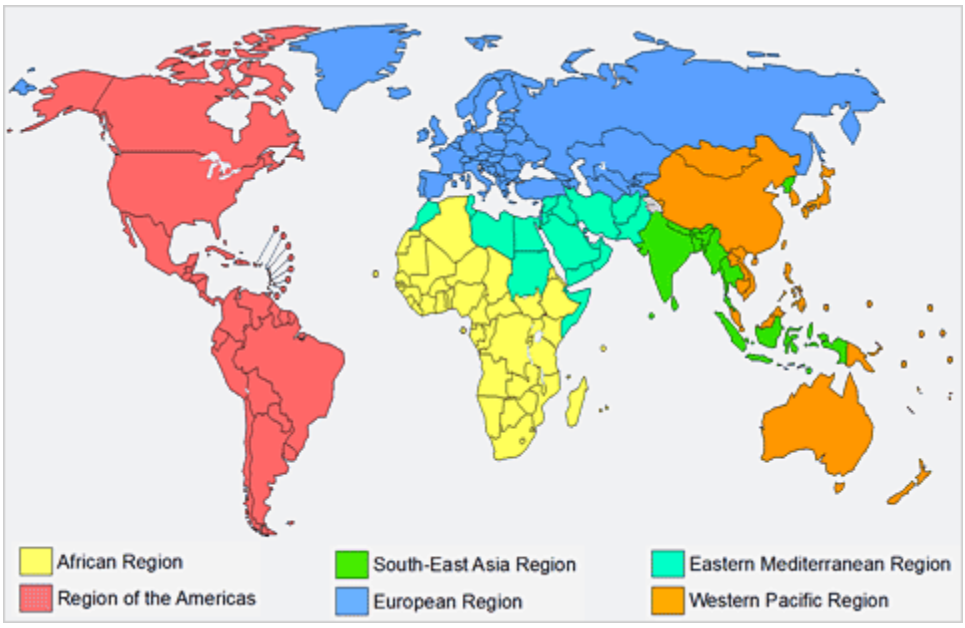


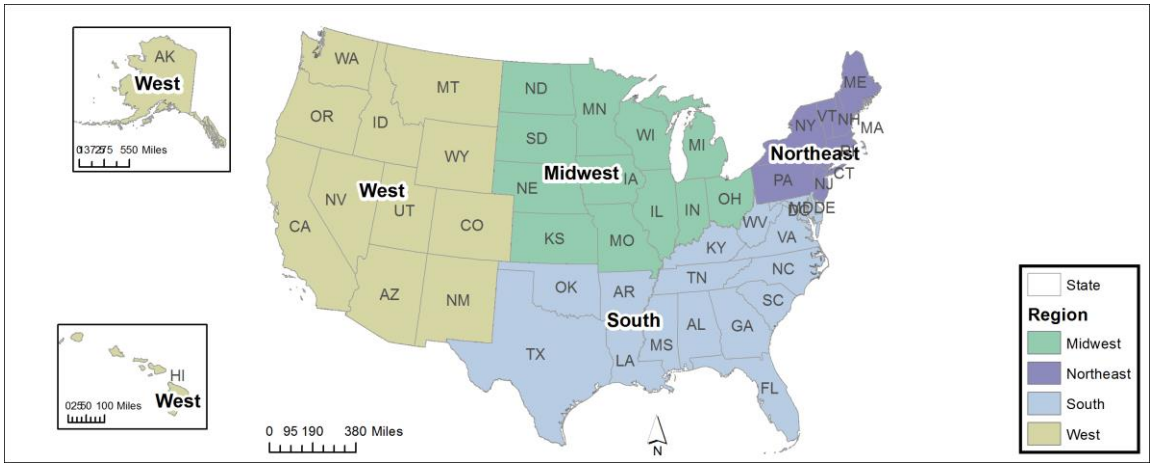
Figure 10: Kaplan-Meier survival curves stratified by alcohol use for individuals diagnosed with Tuberculosis from 2005-2015 in the United States foreign-born population. The vertical axis depicts the survival probability and the horizontal axis represents the years lived in the United States prior to diagnosis.

Appendix

1. Map showing global regions defined by the World Health Organization (WHO).



2. Map showing the U.S. domestic regions defined by the U.S. Census Bureau.



3. SAS coding of how survival time was calculated.

YRSIN_US: Years in U.S.
Extract month & year for years in U.S. calculation

```
IF ORIGIN = 'FBORN';
      IF REPORTDATE NE . AND ARRIVEUSDATE NE . THEN DO;
IF ARRIVEUSDATE > REPORTDATE THEN YRSIN_US = .;
ELSE YRSIN_US = INT((REPORTDATE - ARRIVEUSDATE)
 / 365);
END;
ELSE IF REPORTDATE NE . AND ARRIVEUSDATE = . AND
USMONTH NE ' ' AND USYEAR NE '    ' THEN DO;
IF MDY(USMONTH,1,USYEAR) > REPORTDATE THEN
YRSIN_US = .;
ELSE YRSIN_US = INT((REPORTDATE - MDY(USMONTH,1,
USYEAR)) / 365);
END;
ELSE IF REPORTDATE = . AND ARRIVEUSDATE NE . AND
RPTMONTH NE ' ' AND RPTYEAR NE '    ' THEN DO;
IF ARRIVEUSDATE > MDY(RPTMONTH,1,RPTYEAR) THEN
YRSIN_US = .;
ELSE YRSIN_US = INT((MDY(RPTMONTH,1,RPTYEAR) - ARRIVEUSDATE) / 365);
END;
ELSE IF REPORTDATE = . AND ARRIVEUSDATE = . AND
RPTMONTH NE ' ' AND RPTYEAR NE '    ' AND USMONTH NE ' '
AND USYEAR NE '    ' THEN DO;
IF MDY(USMONTH,1,USYEAR) > MDY(RPTMONTH,1,
RPTYEAR)  THEN YRSIN_US = .;
ELSE YRSIN_US = INT((MDY(RPTMONTH,1,RPTYEAR) -
MDY(USMONTH,1,USYEAR)) / 365);
END;
ELSE YRSIN_US = .;
```